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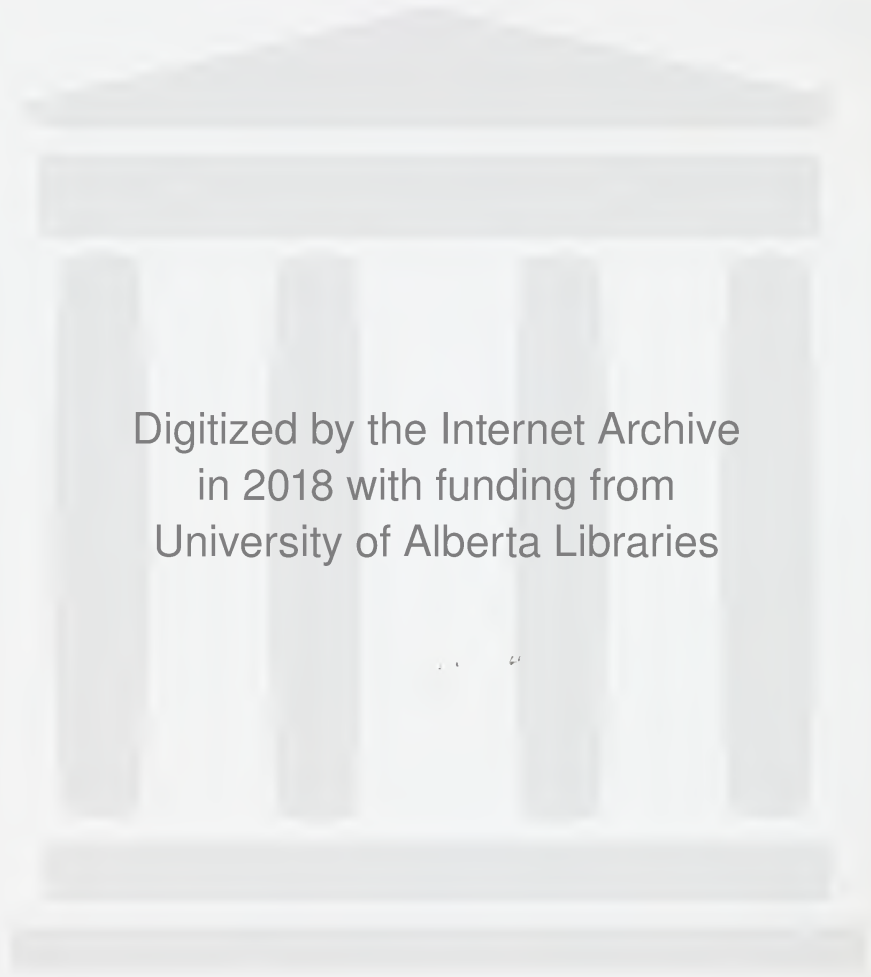
An investigation of some Isomers...
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AN INVESTIGATION OF SOME ISOMERS OF
3, 5 - DIIDO -4- (4'- METHOXY PHENOXY)
NITROBENZENE AND A FEW DERIVATIVES OF EACH

by

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University of Alberta

A THESIS

Submitted to the Committee on
Graduate Studies, University of
Alberta, in partial fulfilment
of the requirements for the
degree of Master of Science.

Edmonton, Alberta

April, 1930

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AN INVESTIGATION OF SOME ISOMERS OF
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NITROBENZENE AND A FEW DERIVATIVES OF EACH

The subject of this investigation was suggested by the synthesis of thyroxine by C. R. Harington and G. Barger¹.

In their synthesis, hydroquinone monomethyl ether was used together with 3, 4, 5 triiodo nitrobenzene. This prompted the idea that the two isomers of the former substance namely guaiacol and resorcinol monomethyl ether, might likewise be linked with the triiodo nitrobenzene. It was further anticipated that the substances thus produced would undergo similar reactions to those found in the synthesis of thyroxine and, eventually, two isomers of thyroxine would result.

Of course it must be realized that this would be an extensive field of investigation and, therefore, it was found necessary to limit the field for this report. It was decided to prepare 3, 5 - diiodo -4- (2'-methoxy phenoxy) nitrobenzene and 3, 5 - diiodo -4- (3'-methoxy phenoxy) nitrobenzene; to reduce these to the

1. C. R. Harington and G. Barger, Biochem. J. 21,
169 (1927).

THE HISTORY OF THE

REIGN OF

CHARLES THE FIRST

BY

JOHN BURNET

OF THE UNIVERSITY OF OXFORD

IN TWO VOLUMES

THE SECOND VOLUME

CONTAINING

THE HISTORY OF THE

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corresponding amines and then form the hydrochloride, the acetyl and the benzoyl derivatives of the amines. This is, then, a report of the investigation completed to this stage.

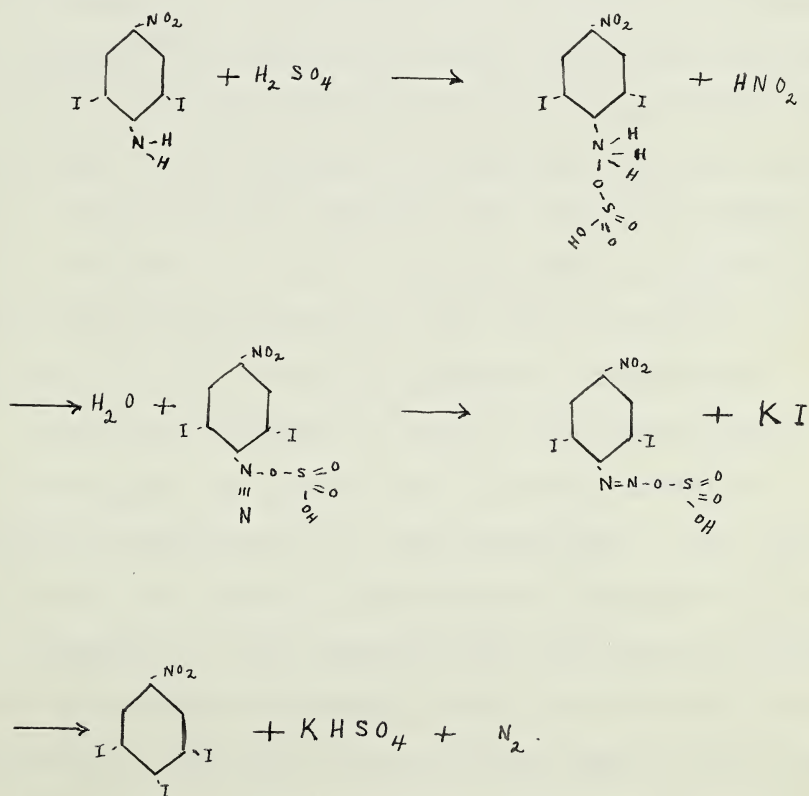
The most convenient starting point for the problem was the preparation of 3, 5 - diiodo para nitroaniline. The amino group in this compound lends itself to diazotization and later substitution by an iodine atom which, owing to the para nitro group, is comparatively active. The compound was obtained by an adaptation of the method of Willgerodt and Arnold². P - nitroaniline is dissolved in acetic acid and treated with iodine chloride:-



For the preparation of 3, 4, 5 triiodo nitrobenzene an adaptation of the method of Harington and Barger¹ was found necessary. These men dissolved the 3, 5 - diiodo - p - nitroaniline in concentrated sulphuric acid, diazotized by means of sodium nitrite, and substituted iodine

2. Willgerodt and Arnold, Ber., 34, 3344 (1901).

by means of potassium iodide. It was found that at the temperature used $5 - 10^{\circ}$, that the concentrated acid did not have sufficient action in liberating nitrous acid. Better results were obtained by diluting the sulphuric acid to such a point that the 3, 5 - diiodo - p - nitro-aniline just remained in solution. The reaction then was:-



The linkage of the 3, 4, 5 triiodo nitrobenzene with guaiacol monomethyl ether or resorcinol monomethyl ether depends on the activity of the iodine atom in para position to the nitro group. One fact to be borne in mind here, is the danger of replacing this iodine by an hydroxyl group unless care is taken that the conditions of the experiment are anhydrous.

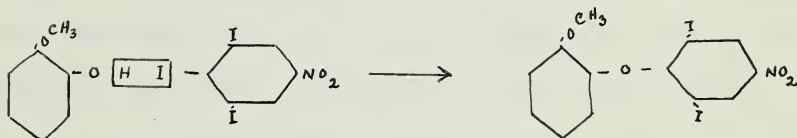
Both ethers were linked to the 3, 4, 5 triiodo nitrobenzene in accordance with the method of Harington and Barger.¹ The ether and benzene derivative were dissolved in boiling ethyl methyl ketone and refluxed for some time in the presence of anhydrous potassium carbonate. In the case of guaiacol the resulting product is 3, 5 - diiodo - 4 - (2' - methoxy phenoxy) nitrobenzene; with resorcinol monomethyl ether the product is 3, 5 - diiodo - 4 - (3' - methoxy phenoxy) nitrobenzene.

The yield obtained in each of the above cases tended to suggest the possibility of steric hindrance. In repeated preparations of these substances, only about one third the yield of the guaiacol compound was obtained, compared to that produced when Harington and Barger¹ used hydroquinone monomethyl ether in their synthesis of thyroxine. This was using the same time or even longer in some cases in the refluxing. Comparing similarly the

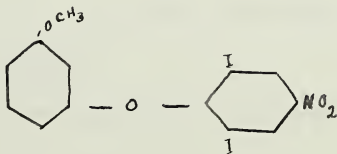
yield of 3, 5 - diiodo - 4 - (3' - methoxy phenoxy) nitrobenzene with their 3, 5 - diiodo - 4 - (4' - methoxy phenoxy) nitrobenzene, the ratio of the yields was found to be approximately one to two.

An effort was made to increase the yield through the use of one g. of copper as a catalyst, an adaptation of the Ullmann reaction. The yield was even further decreased.

The reaction for this step in the problem is, in case of guaiacol and 3, 4, 5 triiodo nitrobenzene:-



Similarly the product in the case of resorcinol monomethyl ether is:-

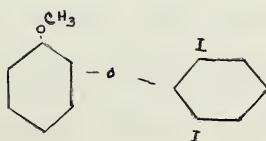


For the reduction of these nitro compounds the method of Harington and Barger¹ was followed again. This consists in dissolving the nitro compound in glacial acetic acid and the use of stannous chloride and hydrogen chloride as the reducing agent. The amine was liberated by means of sodium hydroxide and extracted with ether.

Some care was necessary in this last stage. Both amines were found to oxidize readily in the air producing a somewhat brown colored extract in case of 3, 5 - diiodo - 4 - (2' - methoxy phenoxy) aniline and a pale blue colored one for the 3, 5 - diiodo - 4 - (3' - methoxy phenoxy) aniline. Needless to say the yield is likely to be decreased here, slightly, through this difficulty.

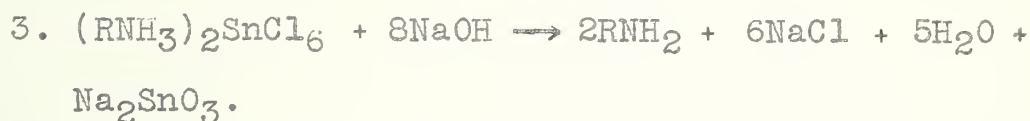
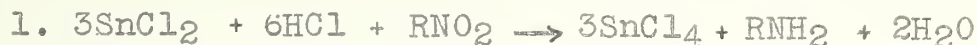
Another interesting fact was the noticeable difference in the solubilities of the amines in the ether; 3, 5 - diiodo - 4 - (3' - methoxy phenoxy) aniline was found much more soluble.

Then, if R represents the group:-



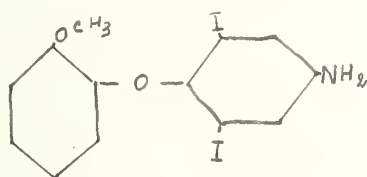


the reactions here are:-

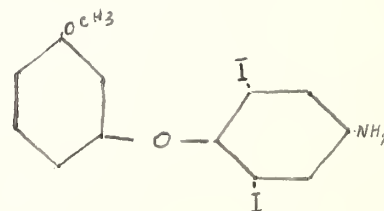


Similar reactions take place with the other amine, the final products being in each case:-

1.

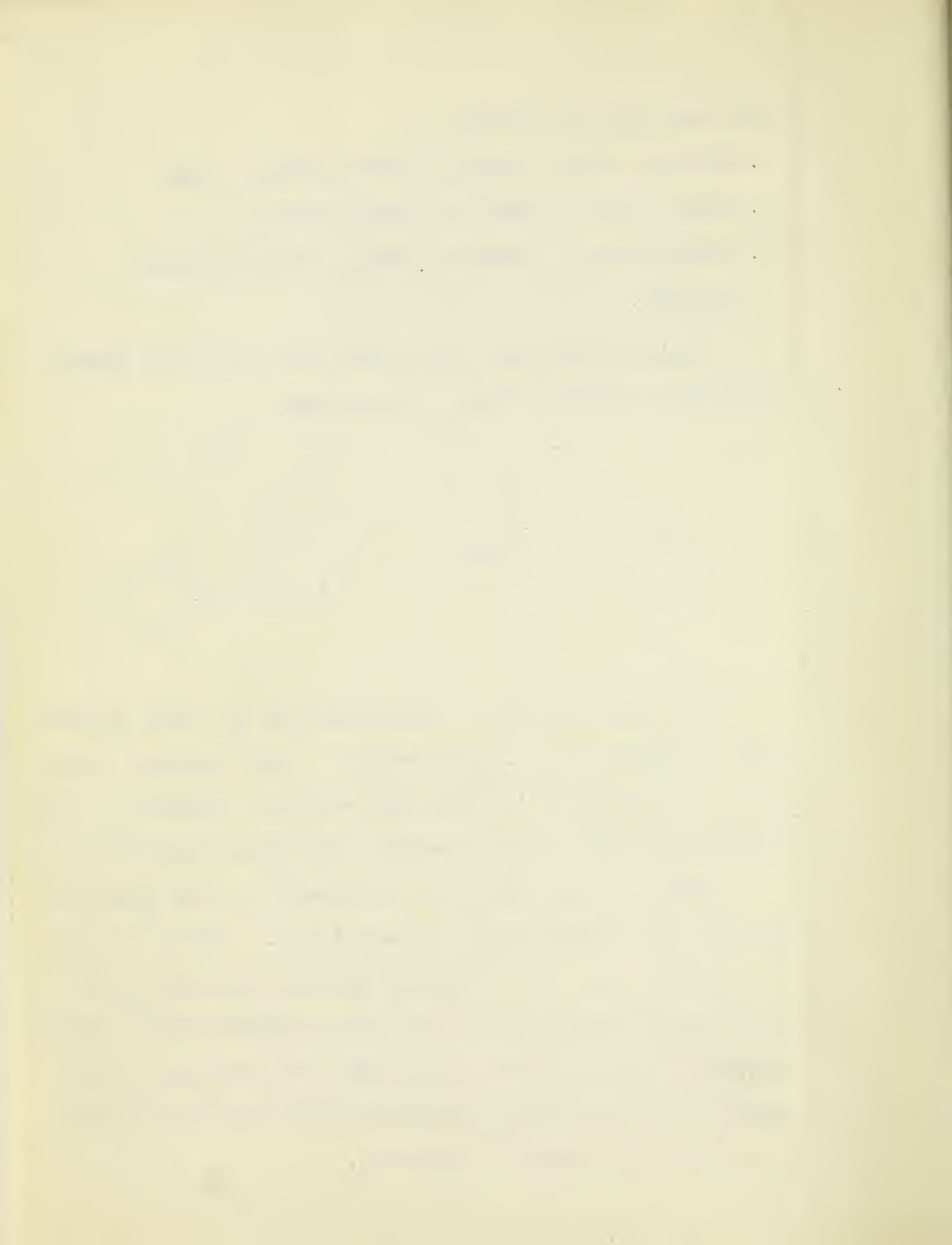


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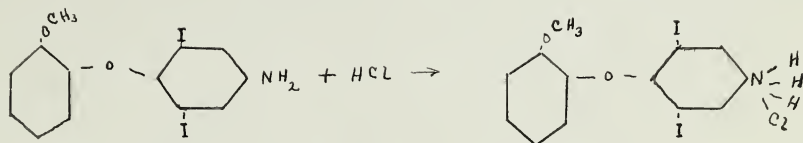


The formation of the hydrochloride of these amines was a comparatively simple matter. Dry hydrogen chloride was introduced into the dry ethereal solution of the amines and their hydrochlorides immediately settled out.

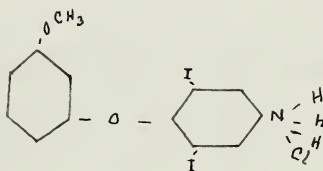
However, one noticeable difference in the behavior of the hydrochlorides may be mentioned. Whereas the 3, 5 - diiodo - 4 - (2' - methoxy phenoxy) aniline formed as a grayish white solid, the other hydrochloride seemed always to separate out in the form of a greenish gray syrup which solidified after the ether was decanted and the syrup was stirred vigorously.



The equation for this reaction, using 3, 5 - diiodo - 4 - (2' - methoxy phenoxy) aniline, is:-

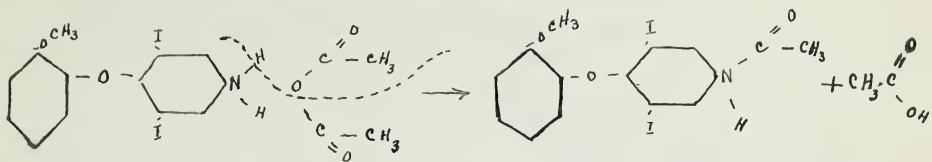


The product with the other amine is:-

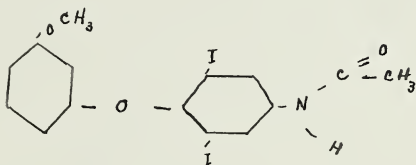


An effort was made to form the acetyl derivatives of these amines using acetyl chloride as the acetylating agent with the amine suspended in water. This method proved unsatisfactory. Much better results were obtained by getting the amine in solution. Fortunately acetic anhydride was found to be a good solvent and acetylating agent at the same time. The reaction and products are:-



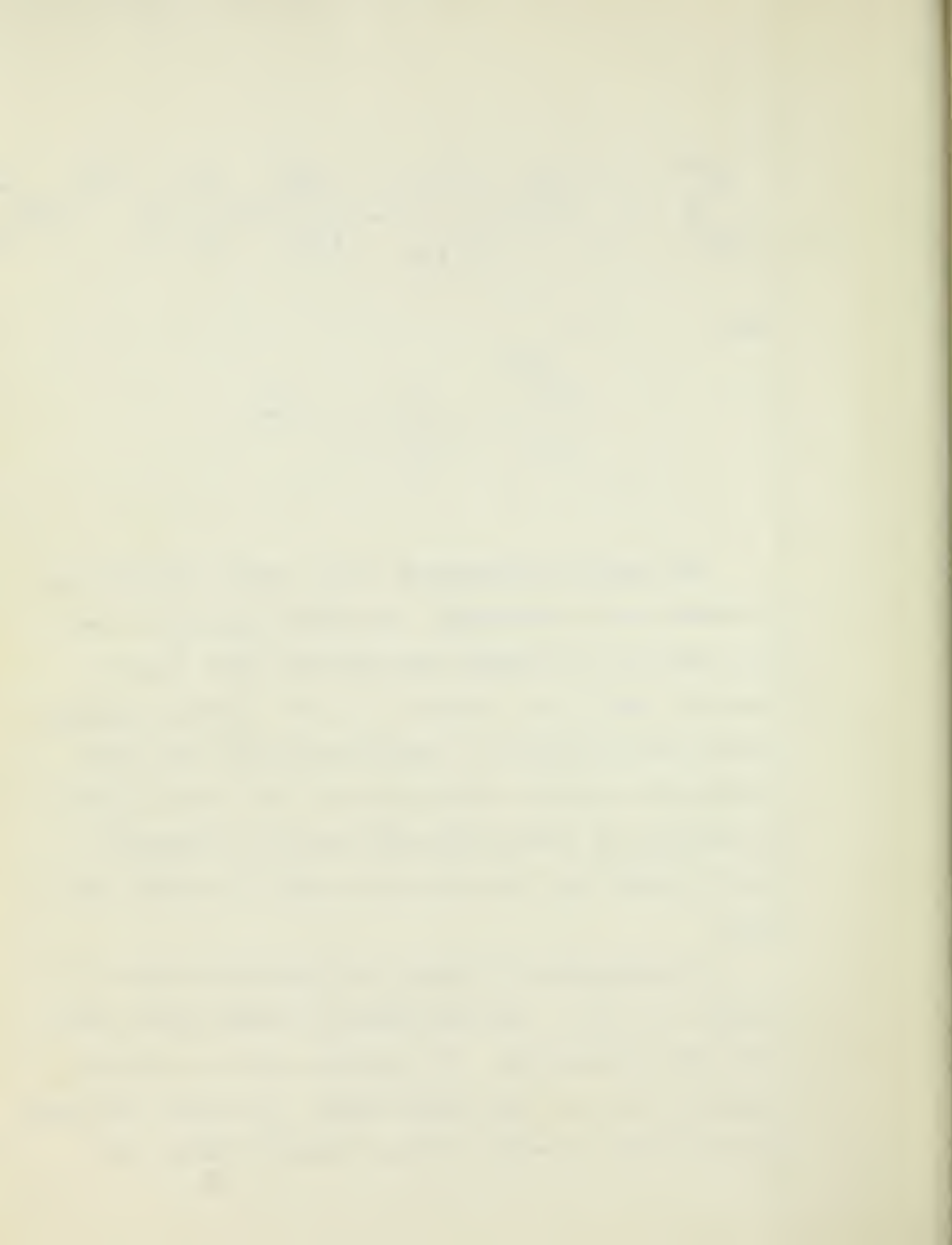


and;



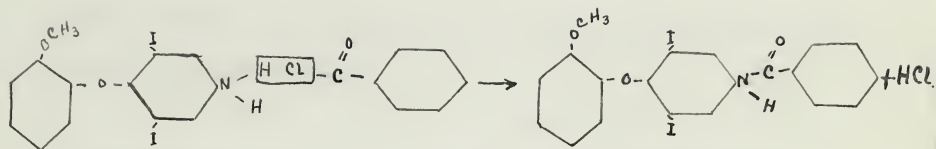
The benzoyl derivatives of the amines offered considerable more difficulty. An effort was made to use the Schotten and Bauman reaction with small success. However, when 3, 5 - diiodo - 4 - (2' - methoxy phenoxy) aniline was dissolved in benzoyl chloride, kept near boiling for sometime, and excess of the latter removed by standing in sodium hydroxide solution overnight, a solid product was obtained which could be readily purified.

On endeavoring to repeat this procedure with 3, 5 - diiodo - 4 - (3' - methoxy phenoxy) aniline great difficulty was encountered. The product, even on repeated recrystallization, was still impure. But when this amine was suspended in water, sodium hydroxide added, then

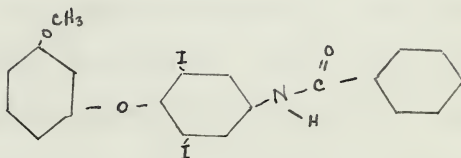


benzoyl chloride, and heated, good results were obtained.

Again the reaction and products are:-



and;



EXPERIMENTAL PART

Preparation of 3, 5- Diiodo-Para-Nitroaniline.- 50 g. para nitroaniline were dissolved in 300 cc. of glacial acetic acid and heated to a temperature of 60-80°. Iodine monochloride (4 mols.) dissolved in 200 cc. of glacial acetic acid, heated to 50°, was added. The mixture was heated on a water bath for two hours, allowed to cool, filtered and washed with glacial acetic. The yellow crystalline product melted at least four degrees higher than that obtained when Willgerodt and Arnold's²

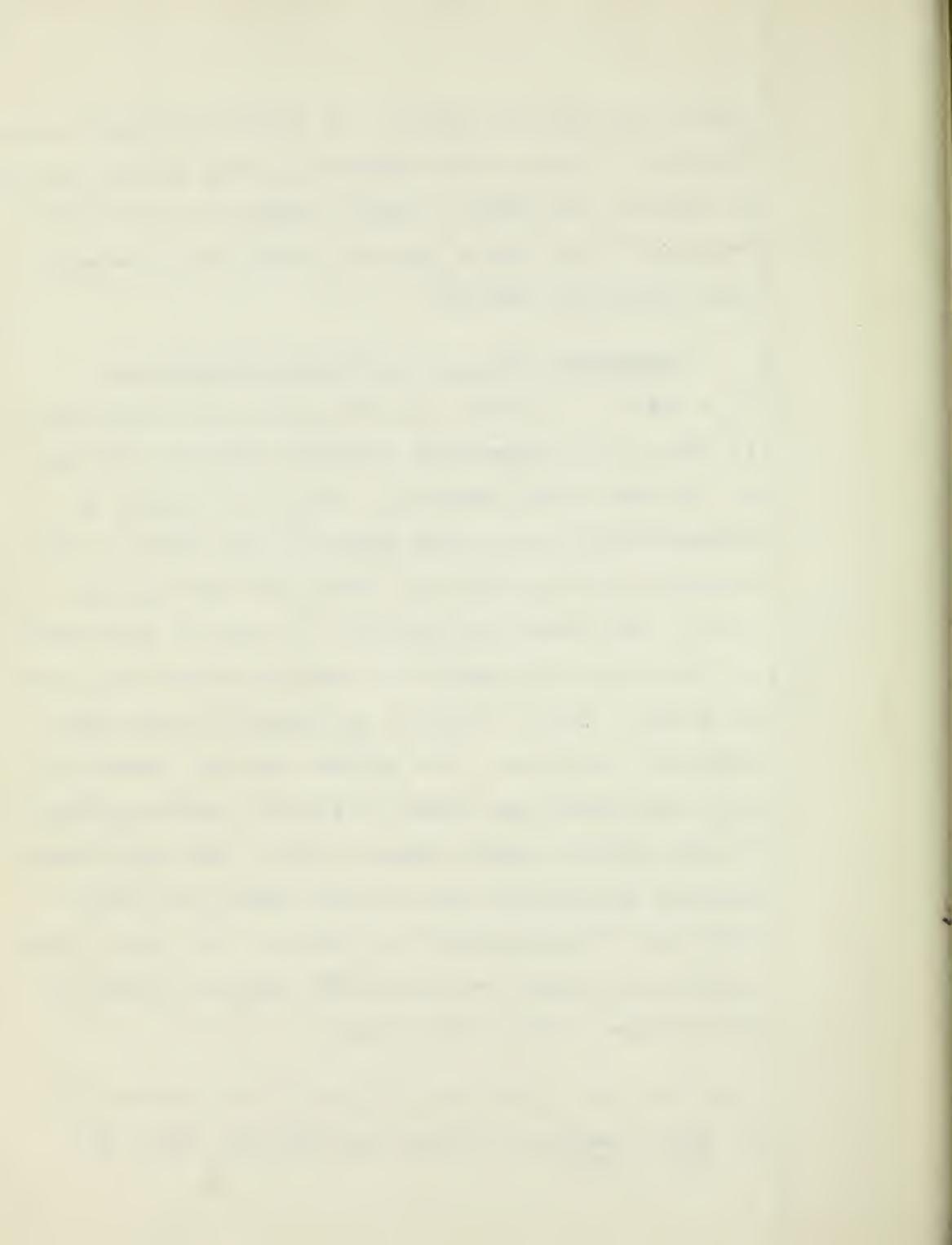


method was followed rigidly. It needed no further purification. The use of an excess of iodine chloride is to be found in the method of Kalb, Schweizer, Zellner and Berthold.³ There was a yield of 80-85% of yellow crystals melting at 243-244⁰.

Preparation of 3, 4, 5 Triiodo Nitrobenzene. -

75 g. of 3, 5 - diiodo -p- nitroaniline were dissolved in 450 cc. of concentrated sulphuric acid and 135-140 cc. of water added gradually. 34 g. (2.5 mols.) of sodium nitrite were slowly added to this solution with constant stirring while the temperature was kept at 5-10⁰. The mixture was stirred for three to four hours. At the end of this period the reaction mixture was poured on ice. 160 g. (5 mols.) of potassium iodide were added with stirring. This mixture was then heated on a water bath until gas ceased to evolve. Sodium bisulphite was added to remove excess iodine. The light brown granular precipitate was filtered, washed with water, dried and recrystallized from acetone. The light yellow crystalline product melted at 165⁰, giving a yield of pure product, 74% of theoretical.

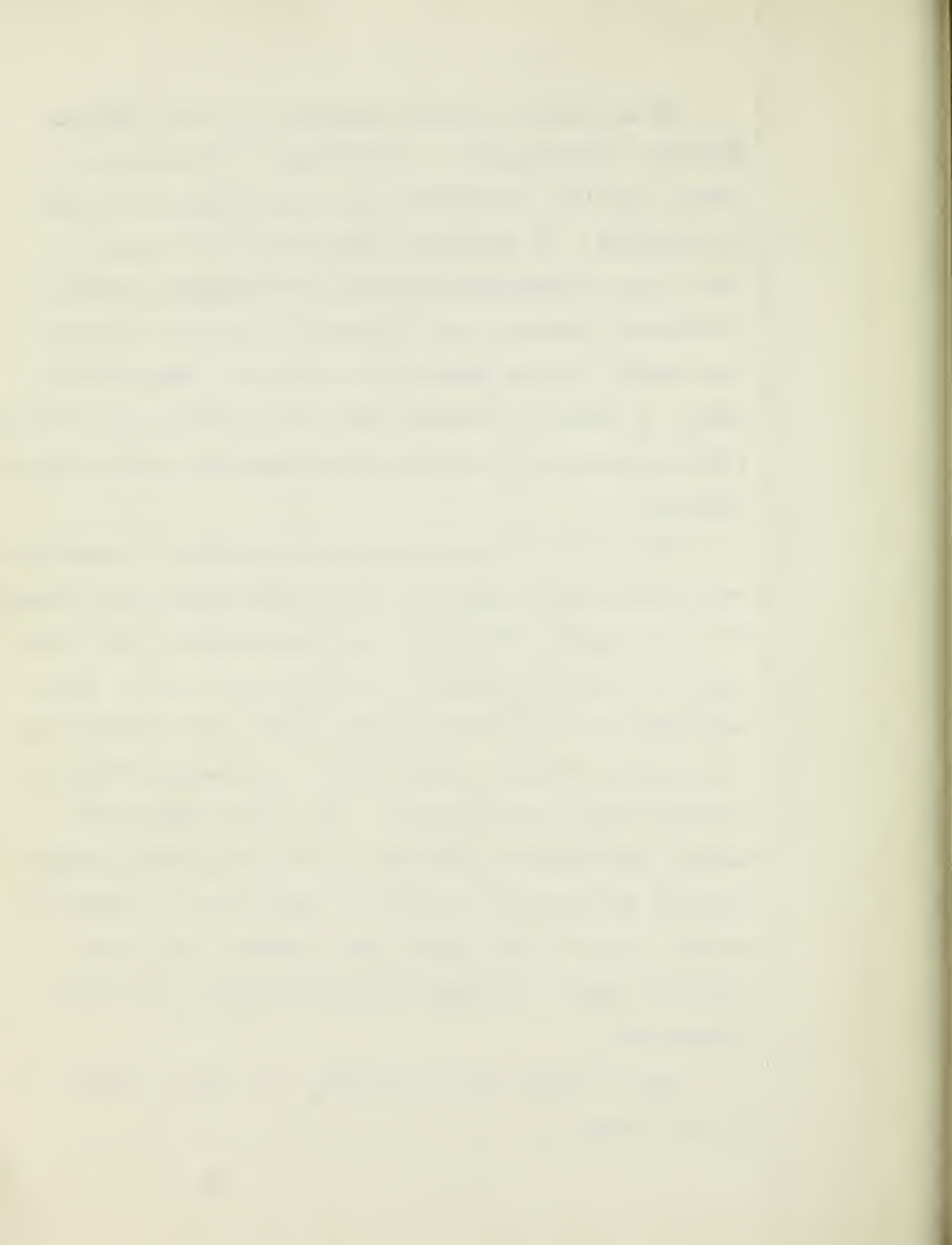
3. Kalb, Schweizer, Zellner and Berthold, Ber., 59, 1869 (1926).



Preparation of 3, 5 - Diiodo - 4 - (2'- Methoxy Phenoxy) Nitrobenzene. - According to Harington and Barger¹ certain precautions in their preparation must be observed. If molecular proportions were used, a good deal of unchanged triiodo nitrobenzene, difficult to remove, resulted, and therefore, twice the theoretical amount of the phenol and potassium carbonate were used. A further precaution was taken to have the methyl ethyl ketone and the carbonate dry and the latter finely powdered.

50 g. of triiodo nitrobenzene and 25 g. of guaiacol were dissolved in 250 cc. of boiling methyl ethyl ketone; 30 g. of finely powdered potassium carbonate were added and the solution refluxed for thirty two hours. Water was added and the solution made acidic with acetic acid. The excess of methyl ethyl ketone and guaiacol were removed by steam distillation. The solid residue was washed with sodium hydroxide solution and then recrystallized from acetone or glacial acetic acid. There resulted a light grey crystalline product, melting at 149-150° (corr.) giving a yield of 10-12 g. or 24% of theoretical.

Anal. Calcd. for $C_{13}H_9O_4NI_2$: I, 51.1. Found: I, 51.17, 51.44.

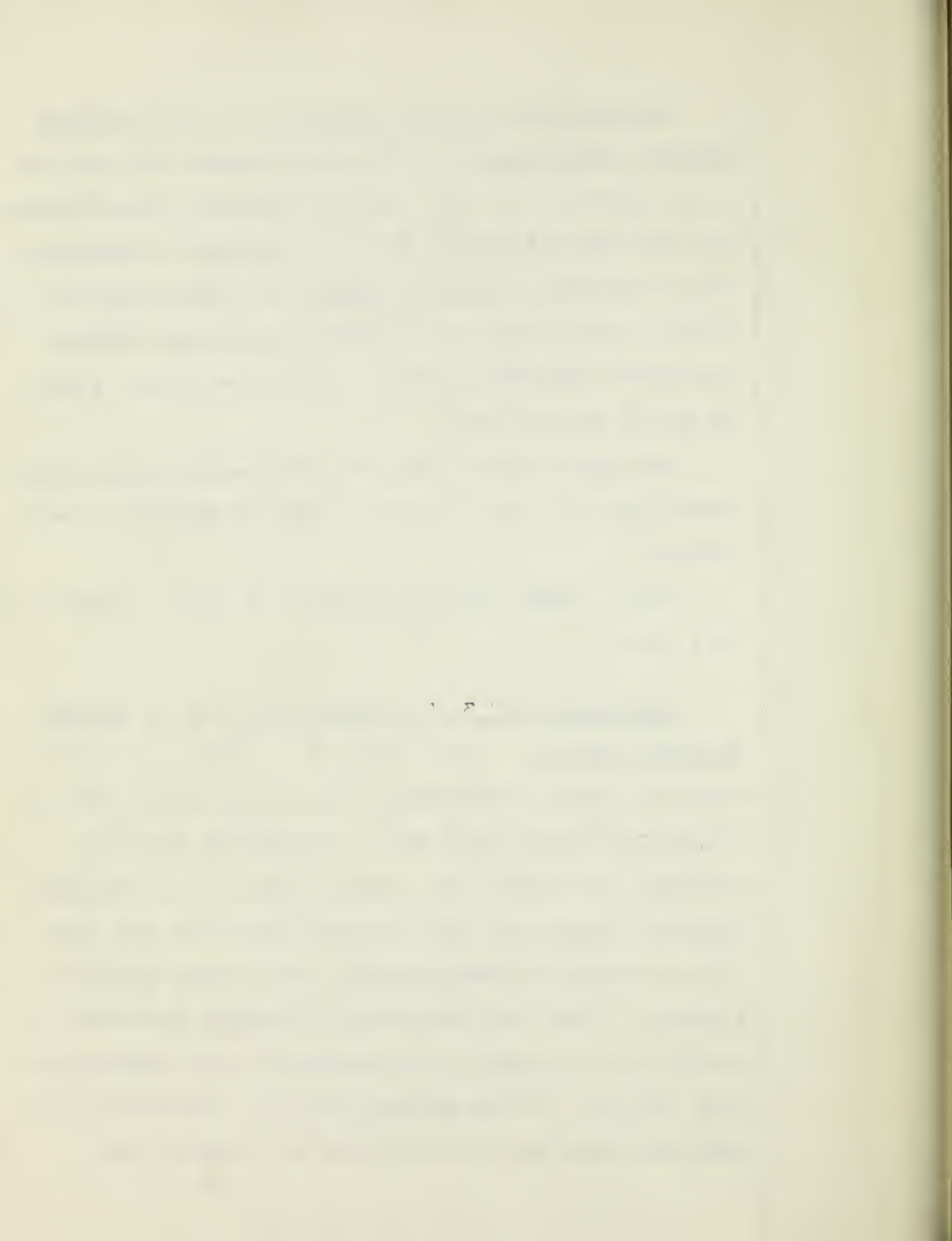


Preparation of 3, 5 - Diiodo - 4 - (3' - Methoxy Phenoxy) Nitrobenzene. - This was prepared the same as 3, 5 - diiodo - 4 - (2' - methoxy phenoxy) nitrobenzene with the exception that 25 g. of resorcinol monomethyl ether was used in place of guaiacol. There resulted 15-18 g. (as a rule) of a yellow crystalline product melting at 139-140° (corr.). This represents a yield of 30-36% theoretical.

One might mention that on one occasion when double quantities were used a yield of 54% of theoretical was obtained.

Anal. Calcd. for $C_{13}H_9O_4NI_2$: I, 51.1. Found: I, 51.1, 51.3.

Preparation of 3, 5 - Diiodo - 4 - (2' - Methoxy Phenoxy) Aniline. - 25 g. of 3, 5 - diiodo - 4 - (2' - methoxy phenoxy) nitrobenzene were dissolved in 125 cc. of glacial acetic acid; 40 g. of powdered stannous chloride were added and a rapid stream of dry hydrogen chloride passed into the solution which was kept hot. After a time the stannichloride of the base began to separate. When the precipitate no longer increased in amount and the solution was saturated with hydrochloric acid (1½ hrs.) it was allowed to cool. The crystalline stannichloride was then filtered off, washed with



glacial acetic, and decomposed, as rapidly as possible, by grinding with 250 cc. of 40% sodium hydroxide solution. The base was immediately extracted with ether and dried over anhydrous sodium sulphate.

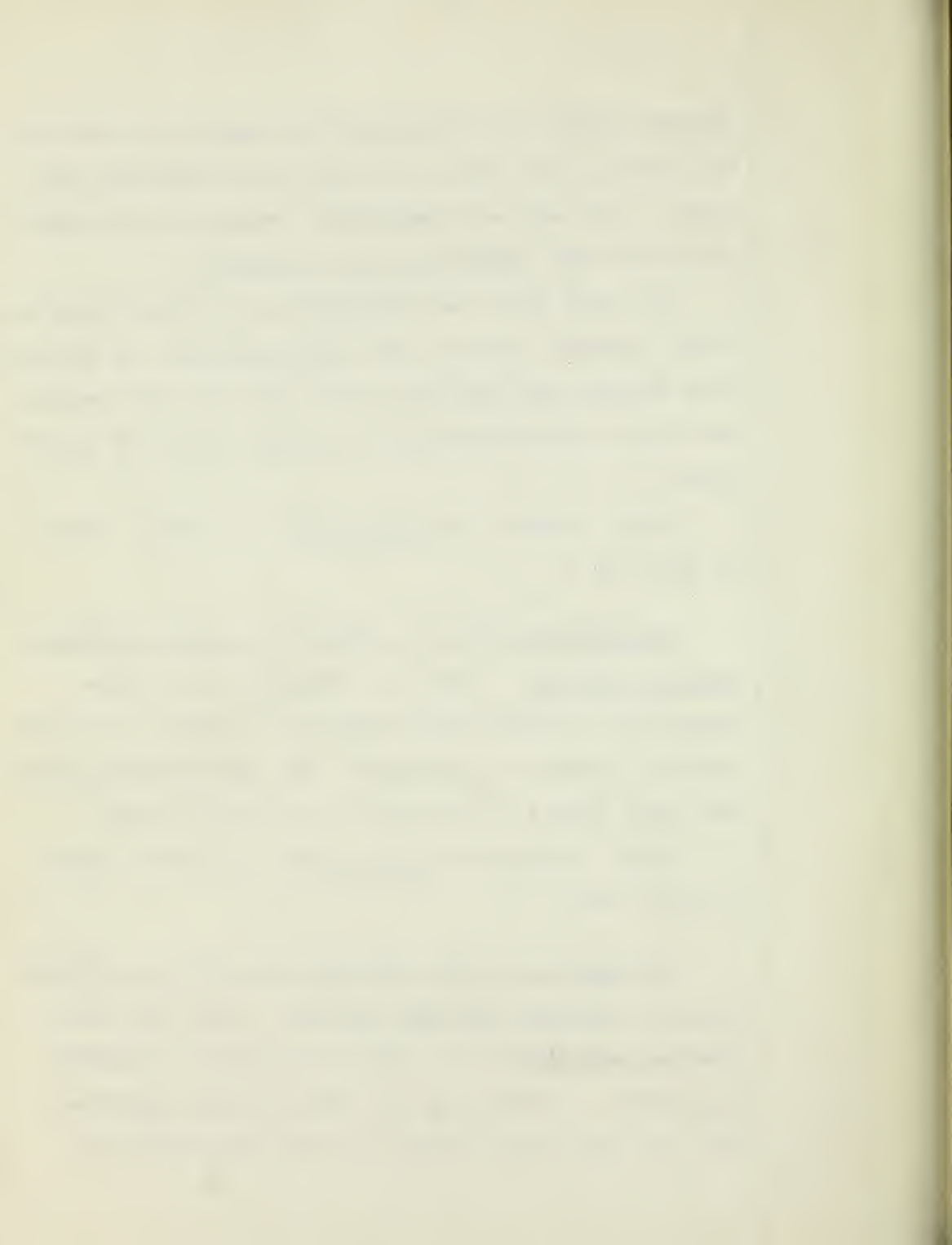
The free base was obtained pure by evaporating the dried ethereal solution and recrystallizing the residue from benzene and petroleum ether and then from benzene. The light colored crystalline product melted at $178-9^{\circ}$ (corr.)

Anal. Calcd. for $C_{13}H_{11}O_2NI_2$: I, 54.4. Found: I, 54.3, 54.7.

Preparation of 3, 5 - Diiodo - 4 - (3' - Methoxy Phenoxy) Aniline. - This was obtained in the same manner as the above amine from 3, 5 - diiodo - 4 - (3'-methoxy phenoxy) nitrobenzene. The crystalline product was light pink in color melting at $124-5^{\circ}$ (corr.).

Anal. Calcd. for $C_{13}H_{11}O_2NI_2$: I, 54.4. Found: I, 54.3, 54.2.

Preparation of the Hydrochloride of 3, 5 - Diiodo - 4 - (2' - Methoxy Phenoxy) Aniline. - Into the dried ethereal solution of the amine dry hydrogen chloride was passed. Immediately the hydrochloride separated out. It was greyish white in color and melted with



decomposition at $236-7^{\circ}$ (corr.)

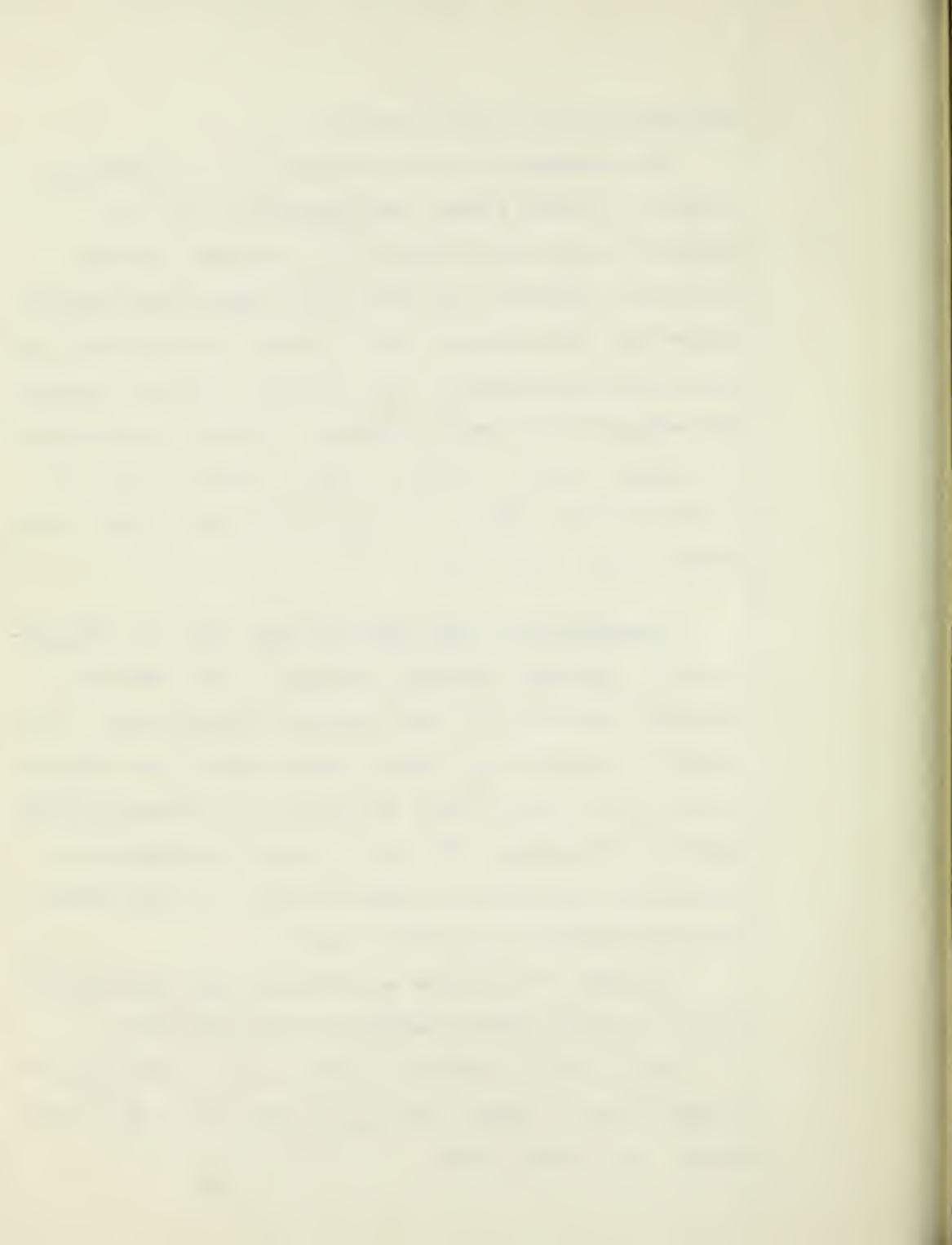
The hydrochloride was analysed by a volumetric method. A known weight was suspended in 100 cc. neutral alcohol and titrated with standard sodium hydroxide solution (CO_2 free) with phenolphthalein as indicator. The results were a little low owing to the fact that the compound to be analysed oxidizes readily and makes the end point somewhat difficult to determine.

Anal. Subs., 2.1093, 0.5970: 35.5, 10 cc. of 0.1163 N.NaOH. Calcd. for $\text{C}_{13}\text{H}_{11}\text{O}_2\text{NI}_2\cdot\text{HCl}$: HCl, 7.24, Found: HCl, 7.14, 7.08.

Preparation of the Hydrochloride of 3, 5 - Diiodo-4 - (3' - Methoxy Phenoxy) Aniline. - This was also prepared similarly to the previous hydrochloride. The product, as mentioned before, separates in the form of a light green syrup which solidifies on decantation of ether and stirring. The solid product is darker in color than the previous hydrochloride. It also melts with decomposition at $132-4^{\circ}$ (corr.).

Analysed in the same way it gave high results owing to an even greater masking of the end point.

Anal. Subs., 0.5850, 0.6688: 10.1, 11.65 cc. of 0.1163 N.NaOH. Calcd. for $\text{C}_{13}\text{H}_{11}\text{O}_2\text{NI}_2\cdot\text{HCl}$: HCl, 7.24, Found: HCl, 7.32, 7.37.



Preparation of 3, 5 - Diiodo - 4 -(2' - Methoxy Phenoxy) Acetanilide. - About 1 g. is dissolved in 10-15 cc. of acetic anhydride heated to boiling and kept near that temperature for three quarters of an hour. On cooling, the acetyl derivative separates out. The excess acetic anhydride is decomposed by the addition of water and boiling. The pure substance is obtained by recrystallization from glacial acetic acid. It is crystalline and almost white in color, melting at $227-8^{\circ}$ (corr.).

Anal. Calcd. for $C_{15}H_{13}O_3NI_2$: I, 49.9. Found: I, 49.8, 49.7.

Preparation of 3, 5 - Diiodo - 4 -(3' - Methoxy Phenoxy) Acetanilide. - This is by a similar method to the above. The product is recrystallized from dilute acetic acid. It is white in color and melts at $177-8^{\circ}$ (corr.).

Anal. Calcd. for $C_{15}H_{13}O_3NI_2$: I, 49.9. Found: I, 49.7, 50.2.

Preparation of the Benzoyl Derivative of 3, 5 - Diiodo - 4 -(2' - Methoxy Phenoxy) Amine. - About 1 g. of 3, 5 - diiodo - 4 -(2' - methoxy phenoxy) aniline was dissolved in approximately 10 cc. of benzoyl chloride.

The solution was heated to boiling and kept near that temperature for three quarters of an hour. Sodium hydroxide solution (conc.) was added and the syrup left standing in this overnight when it solidified. The solid was recrystallized from alcohol giving white crystals, melting at $239-40^{\circ}$ (corr.).

Anal. Calcd. for $C_{20}H_{15}O_3NI_2$: I, 44.4. Found: I, 44.4, 44.6.

Preparation of the Benzoyl Derivative of 3, 5 - Diiodo - 4 -(3' - Methoxy Phenoxy) Amine. - Approximately 1 g. of the corresponding amine was suspended in 20 cc. of water and a little dilute sodium hydroxide solution added. About 5 cc. of benzoyl chloride was poured into the suspension. Alternate application of heat, sodium hydroxide solution and benzoyl chloride produced a syrup which, on standing in alkali overnight, solidified. The solid must be broken up owing to occluded benzoyl chloride. The product recrystallized from alcohol gave pure white crystals, melting at $201-2^{\circ}$ (corr.).

Anal. Calcd. for $C_{20}H_{15}O_3NI_2$: I, 44.4. Found: I, 43.9.

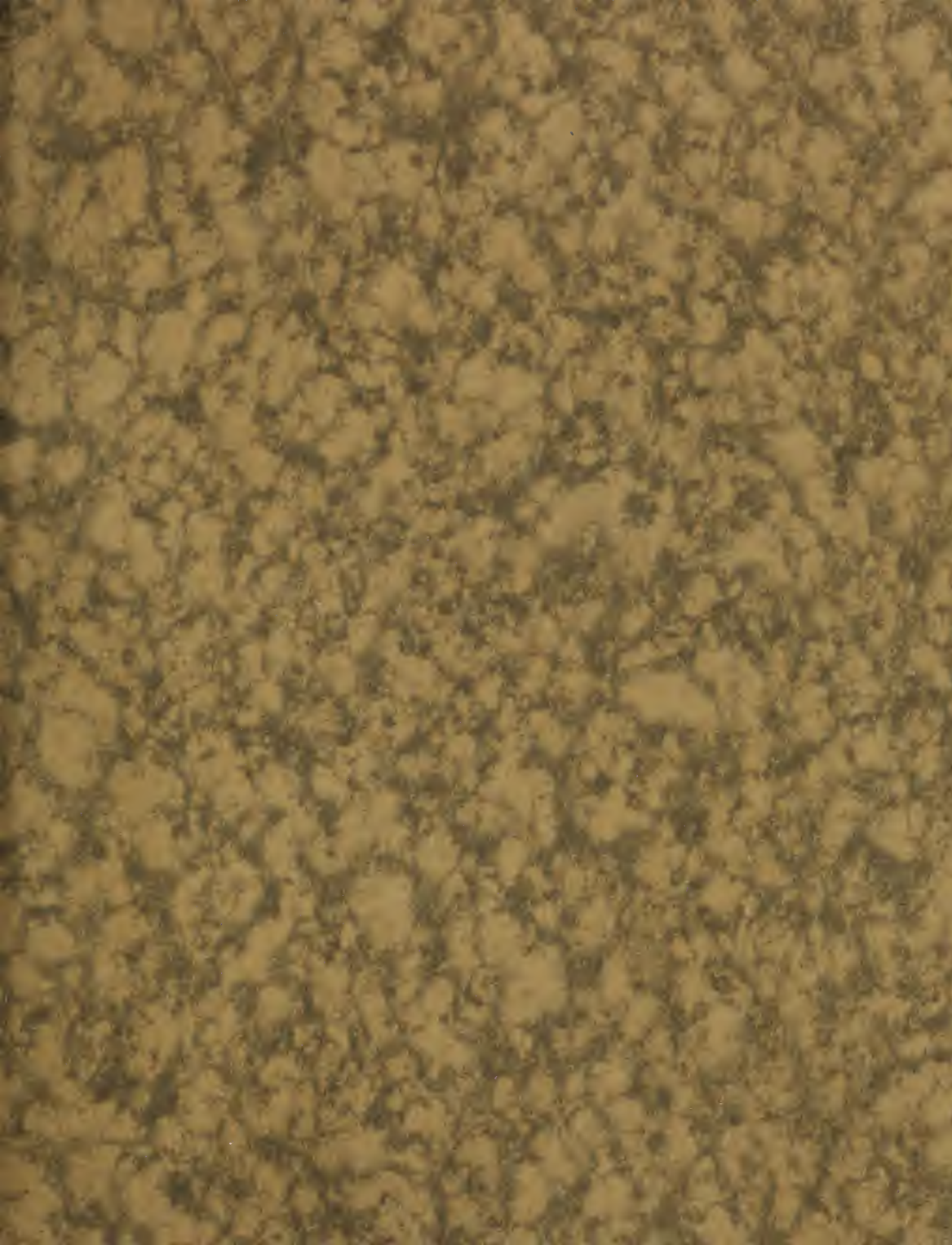
SUMMARY

The following compounds have been prepared and studied: 3, 5 - diiodo -4- (2'- methoxy phenoxy) nitrobenzene; 3, 5 - diiodo -4- (2'- methoxy phenoxy) aniline; 3, 5 - diiodo -4- (2'- methoxy phenoxy) aniline hydrochloride; 3, 5 - diiodo -4- (2'- methoxy phenoxy) acetanilide; and the benzoyl derivative of 3, 5 - diiodo -4- (2'- methoxy phenoxy) amine.

A second group has likewise been prepared: 3, 5 - diiodo -4- (3'- methoxy phenoxy) nitrobenzene; 3, 5 - diiodo -4- (3'- methoxy phenoxy) aniline; 3, 5 - diiodo -4- (3'- methoxy phenoxy) acetanilide; and finally, the benzoyl derivative of 3, 5 - diiodo -4- (3'- methoxy phenoxy) amine.

In conclusion, the author wishes to express his gratitude to Dr. R. B. Sandin, for his helpful suggestions and assistance with this problem.





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